ABSTRACT (or summary) OF RESULTS

a. Since Start of Project. This portion of the summary covers a period from July 1, 1951 to January 1, 1953. As stated above, the objective of the project is to find a synthetic drug which is as effective and as safe from the point of view of human toxicity and addiction liability as is codeine. The drug is needed because, although adequate synthetic substitutes for morphine are available, no such drug of the codeine type is available. Since 75 per cent of the needs for narcotics are for codeine rather then for morphine, this means that we must continue to import and stockpile opium until an adequate substitute for codeine has been developed. The role of the NIMH Addiction Research Center in this research is related to studying the addiction liabilities of new drugs. The evaluation of analgesic and antitussive effects necessarily must be made elsewhere.

Methods used in studying addiction liabilities of the new analgesics have been described in detail in the project descriptions and in previous progress reports. Drugs to be studied are recommended as promising by the Committee on Drug Addiction and Narcotics of the National Research Council. When such drugs are received, the human pharmacology of the compound, which includes determination of its effects on blood pressure, respiratory minute volume, temperature, pupillary size, etc., is carried out. After this is completed, the effects of the drug on the behavior of former morphine addicts

are evaluated by administering the drug in amounts based on the results obtained in the pharmacological experiments. If the drug induces behavior resembling that seen after morphine or codeine, it is likely to have addiction liability. The ability of the drug to relieve and to prevent the appearance of symptoms of abstinence from morphine is next studied in patients strongly addicted to morphine. If the drug relieves or suppresses abstinence, it is judged to have addiction liability. In such experiments, the dose required to relieve or suppress abstinence, and the degree of relief or suppression, are indices for comparison with the standard drug, codeine.

When an especially promising drug is available, it is studied by the direct addiction technic. This involves the administration of ascending doses to former addict volunteers over periods of time ranging between 30 to 180 days. During the addiction period, suitable measurements are carried out to detect and evaluate the development of tolerance. Finally, drugs are withdrawn abruptly and observations for development of abstinence symptoms made.

The drugs studied between 1 July 1951 and 1 January 1953 included d and l Dromoran, d and l 3-methyl ether of Dromoran, dl, d and l 2,2-diethylaminoethyl valerate, dl 2,2-diphenyl-4-dimethylamino butyrate, 3-ethylamino 1:1-(2' dithienyl)-but-1-ene hydrochloride, and 3-diethylamino 1:1 (2' dithienyl)-but-1-ene hydrochloride.

The following drugs are found to have either too high toxicity or too great addiction liability to be considered as possible substitutes for codeine: l Dromoran, l 3-methyl ether of Dromoran, 3-ethylmethylamino-1:1-(2'dithienyl)-but-1-ene, and 3-diethylamino-1:1 (2'dithienyl)-but-1-ene. The following drugs have sufficiently low toxicity and sufficiently low addiction liabilities to be regarded as potential codeine substitutes: d Dromoran, d 3-methyl ether of Dromoran, dl, d and l 2:2-diphenyl-aminoethyl valerate, dl 2:2-diphanyl-4-dimethylamino butyrate. Of these drugs, the d 3-methyl ether of Dromoran appears to be the most promising and is under clinical test for antitussive value. This compound is, however, known to be ineffective as an analgesic. D Dromoran has been discarded, since it is not an effectivd antitussive. It has been recommended that preliminary clinical testing be begun with d and l 2,2-diphenyl-4-dimethylamino valerate and with dl ethyl-2,2-diphenyl-4-dimethylamino butyrate.

b. Results During Current Reporting Period. During the first six months of the reporting period the project was financed by funds from the National Institute of Mental Health. Since 1 July 1953, it has been financed by the Office of Naval Research. The report includes results obtained during both periods of time.

The methods used were identical with those described above.

The following drugs have been tested:

(1) dl, d and l 2,2-diphenyl-4-dimethylamino valerate. Work with these compounds was completed during the first six months of the year. The results were identical with the tentative results reported in the last progress report. All of these compounds, in doses of 60 to 75 mg., induce slight pupillary constriction, slight respiratory depression, and behavior resembling that seen after the administration of small amounts of morphine. No untoward side effects were observed with the doses used. All of the compounds were relatively ineffective in suppressing abstinence from morphine and are judged to have low addiction liability. The dextrorotatory compound appears to be the most effective. Preliminary clinical testing of the dextro- and levo-rotatory isomers is being recommended to the Drug Addiction Committee.

(2) dl 2,2-diphenyl-4-dimethylamino butyrate. This compound has properties resembling those described under (1) above, but is even less potent. Preliminary clinical trial may be warranted.

(3) 3-ethylmethylamino-1:1-(2'dithienyl)-but-1-ene. This drug is the prototype of a completely new class of synthetic analgesics which was discovered in Great Britain. In doses of 30 to 60 mg., it causes pupillary constriction, depression of

respiratory rate and minute volume, and induces behavior strongly resembling that seen after administration of 15 to 30 mg. of morphine sulfate. The drug is irritating to the skin and is broken down in the body to unknown sulphur-containing compounds which cause marked discoloration of the urine. In some patients, peculiar mental reactions consisting either of hypnogogic delusions or true hallucinations but with maintenance of insight were observed. The drug is very effective in suppressing abstinence from morphine. During a period of 30 days experimental addiction, partial tolerance was developed. Abstinence was precipitated by N-allylnormorphine and, on abrupt withdrawal, a definite abstinence syndrome was observed which resembled abstinence from morphine, except for time course. This drug was judged to be too toxic and to have too high addiction liability to be considered a good substitute for codeine; furthermore, it was relatively ineffective when given orally.

(4) 3-diethylamino 1:1-(2'dithienyl)-but-1-ene. This compound closely resembles compound (3) above. Its properties are almost identical with those of compound (3) and it is not regarded as a promising substitute for codeine.

(5) Alpha-l-methadol. This member of the methadone series is a very potent drug. In doses of 30 to 60 mg. it induces pupillary constriction, respiratory depression, etc. These effects appear quite slowly and are still evident 72 hours following administration of the drug either subcutaneously or orally. It is

extremely effective in suppressing abstinence from morphine. The drug is judged to be too toxic and to have too high addiction liability to be regarded as a promising substitute for codeine.

(6) Beta-d-acetylmethadol. This compound is similar to (5). Its properties are such that it is not regarded as a promising substitute for codeine.

(7) Dextro- and levorotatory 2,N-dimethyl-3-hydroxy-morphinan. The dextrorotatory form of this compound is quite inert in man. It does not produce morphine-like effects and is completely ineffective in relieving and suppressing abstinence from morphine. No untoward toxic effects were observed with doses ranging as high as 75 mg. subcutaneously or orally. The levorotatory form of the drug has morphine-like effects when given in doses of 30 to 60 mg. either hypodermically or orally. It is fairly effective in suppressing abstinence from morphine. The levorotatory form is judged to have greater addiction liability than that of codeine. However, in the event that d methyl Dromoran is not found to be an effective antitussive agent, recommendation for clinical trial of this agent would be warranted, since, as judged by animal testing, it is a very effective antitussive drug.

(8) Mixtures of N-Allylnormorphine and Morphine. Mixtures of these drugs have been studied at the recommendation of the Drug Addiction Committee as the beginning of a program designed to determine whether or not the addiction liability of

the more powerful synthetics can be attenuated by the addition of Nalline or other morphine antagonists without seriously impairing therapeutic effects. The following mixtures have been studied: 1 to 10 (1 mg. Nalline to each 10 mg. morphine), 1 to 5 (1 mg. Nalline to each 5 mg. of morphine), and 1 to 3 (1 mg. Nalline to each 3 mg. of morphine). When administered subcutaneously, development of morphine-like euphoria in former morphine addicts is blocked with all these mixtures for periods ranging between 2 to 3 hours. The higher the proportion of Nalline in the mixture the more effective is the blocking and the longer it persists. Miosis induced by morphine is partly antagonized by these mixtures. Depression of respiratory minute volume, however, is not antagonized when the drugs are administered simultaneously. These mixtures precipitate abstinence or make abstinence more intense, rather than relieve it. During direct addiction experiments, patients on all three mixtures complained bitterly that the drug did not have the desired effects, that it had no "kick" and that it did not make them "high." Despite this, evidence of morphine-like intoxication was observed, including pupillary constriction, excessive somnolence, etc. After a few days of chronic administration of the mixture, profuse sweating would occur after each injection. This would persist for about 20 minutes, only to reappear following the next injection. Patients also complained of weird dreams. On abrupt withdrawal of the mixture, some patients

experienced weird dreams and hallucinations during the first 24 hours of abstinence; thereafter, mild morphine-like abstinence was observed. The intensity of abstinence after withdrawal of the mixtures was less than following withdrawal of morphine.

Experiments with these mixtures have been encouraging. They appear to be relatively safe and they could not be abused by drug addicts, so their addiction liability is judged to be low or non-existent. However, certain drawbacks are apparent: both morphine and Nalline are relatively ineffective when administered orally. It is also unknown whether the unpleasant effects observed during chronic administration of large "addicting" doses would occur if the doses were held in the usual therapeutic range. If this occurs, the mixtures could not be used clinically.

(9) 4-4-Diphenyl-6-Dimethylamino-Hexanone-3. This member of the methadone series induces mild morphine-like effects when administered in doses of 60 mg. either hypodermically or orally. No serious toxic effects have been observed with these large doses. Only transient, slight relief of abstinence was observed following administration of 60 to 75 mg. hypodermically to patients with severe symptoms of withdrawal from morphine. Evaluation of this drug is incomplete, but at the moment it is regarded as possibly very promising from the point of view of low addiction liability.

(10) di, l-methyl-4-phenyl-4-carbothoxy-azocycloheptene. This compound is a member of the demerol series. Doses ranging up to 150 mg. subcutaneously induced neither subjective nor detectable objective effects in nontolerant former morphine addicts. However, when 2 patients who were strongly addicted to morphine received 150 mg. of the drug in a suppressive experiment, serious toxic reactions manifested by dizziness, blurring of vision, anxiety, elevated blood pressure and, in one patient, signs of pulmonary edema ensued. Work with the compound has been suspended pending further animal toxicology at the University of Michigan.

PLANS FOR FUTURE:

Immediate. During the coming six months we hope to complete work on the drugs listed under items (7) through (10) above. In addition, we plan to investigate the properties of the following morphine antagonists: (1) N-Allylnordiacetylmorphine, (2) N-Propyldihydronormorphine, (3) dextrorotatory N-Allylnordromoran, (4) levorotatory N-Allylnordromoran, (5) levorotatory 3-methylether of N-Allylnordromoran. It is hoped that some of these antagonists will be effective orally. In the event that such an antagonist is found, the effects of oral administration of the antagonist when combined with methadone, Dromoran and l 3-methyl ether of Dromoran will be studied in the hope of developing an orally effective mixture of an antagonist (preferably synthetic), together with a potent synthetic and orally effective analgesic drug. Such mixtures should, like mixtures of morphine and Nalline, have

reduced addiction liability. We also plan to open a new approach to the problem and to investigate the possibility of combining codeine with a metabolic blocking agent, beta-diethylaminoethyl-propylacetate. This compound is reported to increase the intensity of effect and the length of action of a number of analgesic drugs. Combining it with codeine would represent one way of increasing the supply of codeine.

Long-range Plans. We intend to continue the search for an adequate substitute for codeine until a drug is found which is judged by the Drug Addiction Committee of the National Research Council to fulfill all the necessary requirements. Only suspension of the project due to lack of funds would cause work to cease prior to the attainment of this goal.

REPORTS AND PUBLICATIONS (During current reporting period)

1. Isbell, H., Fraser, H.F., and Wikler, A.: Addiction Liability of Dithienylbutylamines. Federation Proc., 12: 333 (Mar.) 1953.
2. Isbell, H., and Fraser, H.F.: Actions and Addiction Liabilities of Dromoran Derivatives in Man. J. Pharmacol. & Exper. Therap., 107: 524-530 (Apr.) 1953.
3. Isbell, H., and Fraser, H. F.: Actions and Addiction Liability of the Dithienylbutenylamines in Man. J. Pharmacol. & Exper. Therap., 109: 417-421 (Dec.) 1953.
4. Fraser, H. F., Isbell, H., Vanhorn, G. D., and Nash, T. L.: Use of Measurements of Miotic Effects in Evaluating Analgesic Drugs in Man (Abstract). J. Pharmacol. & Exper. Therap. (In press).

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